Peripheral aneurysms and arteriomegaly: Is there a familial pattern?

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Purpose: **Studies have shown that 11% to 18% of patients with an abdominal aortic aneurysm (AAA) have a first-degree relative with an AAA. A familial pattern among patients with peripheral arterial aneurysms and arteriomegaly has not been reported. The objective of this study was to examine familial patterns among patients with peripheral arterial aneurysm and arteriomegaly and compare them with patterns among patients with AAA.**

Methods: **Pedigrees were constructed for first-degree relatives of patients who received the diagnosis of peripheral arterial aneurysm, arteriomegaly, or AAA from 1988 through 1996. The presence of aneurysms and risk factors was confirmed for patients and relatives by means of telephone interviews and review of hospital and physician records.**

Results: **Seven hundred three first-degree relatives older than 50 years were contacted for 140 probands with peripheral arterial aneurysm, AAA, or arteriomegaly. There were differences in risk factors for hernia and diabetes mellitus among the probands with peripheral arterial aneurysm, AAA, or arteriomegaly but none for relatives. Patients with peripheral arterial aneurysm (n = 40) had a 10% (4/40) familial incidence rate of an aneurysm, patients with AAA (n = 86) had a 22% (19/86) familial incidence rate, and patients with arteriomegaly (n = 14) had a 36% (5/14) familial incidence rate. AAA (24/28, or 86%) was the aneurysm diagnosed most commonly among first-degree relatives. Most aneurysms (85%) occurred among men.**

Conclusion: **There appears to be a gradation of familial patterns from peripheral arterial aneurysm to AAA to arteriomegaly among patients with degenerative aneurysmal disease, and there appears to be a predominance among men. Relatives of patients with any of the 3 lesions—peripheral arterial aneurysm, AAA, arteriomegaly—most frequently have AAA. Relatives of patients with AAA, peripheral arterial aneurysm, or arteriomegaly may be screened by means of a physical examination for peripheral aneurysmal disease. Screening by means of ultrasound examination of the aorta should be limited to first-degree relatives of patients with aortic aneurysms or arteriomegaly. (J Vasc Surg 1998;28:599-605.)**

Abdominal aortic aneurysm (AAA) occurs among approximately 1.5% of the male population older than 50 years[1]; a sharp increase occurs at approximately 55 years of age.[2] Several epidemiologic studies have shown an increased prevalence of AAA among first-degree relatives of patients treated for AAA.[3,4] This information has been used to recommend ultrasound surveillance for men older than 50 years who are relatives of patients with AAA. It also suggests a genetic cause of AAA.[5,6]

Aneurysms of the peripheral arteries (femoral, popliteal, and isolated iliac) are less common than aortic aneurysms,[7] and arteriomegaly (diffuse aneurysmal disease) is even less common.[8] Both peripheral aneurysms and arteriomegaly carry a high risk for complications such as rupture, embolism, or thrombosis.[9] Little epidemiologic information is available to provide guidance to relatives of patients with peripheral aneurysms or arteriomegaly regarding risk for development of aneurysms. Routine screening of relatives of patients with aortic and peripheral aneurysms is not recommended because of the absence of data

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Table I. Aneurysms managed (1988–1996)

Type	*Total*	*No. of pedigrees*	*Percentage*
Abdominal aortic	300	86	29
Iliac	19	10	53*
Femoral	18	14	78*
Femoral pseudoaneurysm	61	0	0
Popliteal	26	20	77*
Arteriomegaly	14	14	100

*Patients excluded died, were not available for follow-up observation, moved, were adopted, or had lost contact with family.

demonstrating that screening is likely to help identify aneurysms or allow early treatment to prevent rupture, thrombosis, or embolization.

The purposes of this study were to examine the prevalence of familial aneurysms among patients with peripheral arterial aneurysms or arteriomegaly, to compare this incidence with that of aortic aneurysms, and to provide recommendations regarding screening of patients with peripheral aneurysmal disease and arteriomegaly.

METHODS

Patients who received the diagnosis of and were treated by means of surgical repair of an aneurysm of the popliteal, femoral, or iliac arteries or for arteriomegaly from 1988 through 1996 were found from medical records at the University of Utah and Salt Lake City Veterans Affairs Hospitals. Patients with anastomotic false aneurysms, instrumentation-induced pseudoaneurysms, or iliac artery aneurysms contiguous with an AAA were excluded. Each patient's medical record was reviewed for location of aneurysms and presence of risk factors, including sex, age, hypertension, hypercholesterolemia, smoking, chronic obstructive pulmonary disease, diabetes, and hernia. Among patients with two or more synchronous aneurysms, the first diagnosed aneurysm was considered to be the primary lesion for evaluation purposes. Each patient (proband) was contacted by letter and telephone to confirm these data and determine whether additional aneurysms were identified. In addition, a pedigree of first-degree relatives (parents, siblings, children) of each patient was constructed. Because previous studies have shown that aneurysmal disease rarely presents before 50 years of age,[10,11] only first-degree relatives older than 50 years were contacted. Data obtained from the first-degree relatives, which included location of all known aneurysms and coexisting risk factors, were confirmed by a member of the investigative team by means of both reviewing the hospital records and conducting telephone interviews. Aneurysms were identified by means of routine physical examination, radiographs, surgical findings, and family tree.

When aneurysms or arteriomegaly was identified in a patient or relative, we used the reporting standards of the Society for Vascular Surgery and International Society for Cardiovascular Surgery to classify aneurysmal disease.[12] A permanent localized (ie, focal) dilatation of an artery and an increase in diameter more than 50% were considered evidence of an aneurysm. Arteriomegaly was defined on the basis of the same criteria as diffuse arterial enlargement involving several arterial segments (ie, nonfocal) with an increase in diameter of more than 50% by comparison to the expected normal diameter. Medical records and radiographic reports of the probands and relatives were reviewed to verify the existence of risk factors or location of aneurysms.

No relative underwent a physical or ultrasound examination for aneurysmal disease solely for the purpose of this study, although many patients and relatives underwent examinations for peripheral or aortic aneurysms initiated by their primary physicians or their surgeons as part of their routine medical and surgical care. Patients and families with incomplete medical records, not available for follow-up data collection, or with insufficient pedigree information were excluded from analysis.

A concurrent epidemiologic survey was conducted on a subset of patients with diagnosed and surgically repaired AAAs who were treated at the University of Utah and Salt Lake City Veterans Affairs Hospitals over the same time period. These patients provided a control for the data-gathering methods. Epidemiologic data on aortic aneurysms were used to compare these data with those from the previously reported study of the familial incidence of AAA.

This study was approved by the University of Utah/Veterans Affairs Hospital institutional review board. All patients and relatives signed a consent form before providing medical information or allowing review of their medical records. Statistical analysis was performed on the data by means of the Fisher exact test for computing two-tailed probabilities. Statistical significance was considered to be the $P < .05$ level.

RESULTS

During the 8-year period, 300 aortic aneurysms and 124 peripheral aneurysms were treated (Table I). Among the peripheral aneurysms were 19 isolated iliac, 18 femoral, 26 popliteal, and 61 femoral pseudoaneurysms. Pseudoaneurysms were excluded from further evaluation. One hundred forty patients

with 86 aortic and 40 peripheral aneurysms and 14 patients with arteriomegaly had sufficient information to allow completion of a family pedigree. Seven hundred three primary relatives of patients with aneurysms were contacted. Each patient had an average of five primary relatives older than 50 years from whom data were obtained.

Probands. The distribution of aneurysms among the probands is shown in Fig 1. Fifty percent of peripheral aneurysms were popliteal. Table II shows a more detailed analysis of the probands. The mean ages at presentation of peripheral aneurysms, arteriomegaly, and AAA were similar. Arteriomegaly and peripheral aneurysms occurred predominantly among men with a male-to-female ratio ranging from 9:1 to infinity. Aortic aneurysms had a lower male-to-female ratio, 5.6. The male-to-female ratio for peripheral aneurysms (43:1) was significantly different (P = .019) than that for AAA (5.6:1). However, the male-to-female ratio for arteriomegaly (13:1) was not significantly different (P = .378) than that for AAA (5.6:1).

Twelve of the patients with peripheral aneurysms (28%) had an anatomically separate AAA identified later. Only 4 of 40 patients with peripheral aneurysms (10%) had another synchronous peripheral aneurysm in spite of routine physical examinations or ultrasound surveillance of peripheral arteries (femoral, popliteal). Thus 38% of the patients with peripheral aneurysms were ultimately found to harbor another aneurysm.

Analysis of risk factors among the probands (Table III) demonstrated that the presence of diabetes and hernia was statistically different for the three groups. Hypertension and smoking were present among more than 60% of the probands in all three groups. The 12 patients with synchronous aortic and peripheral aneurysms had no significant difference in risk factors compared with patients with isolated aortic or peripheral aneurysms.

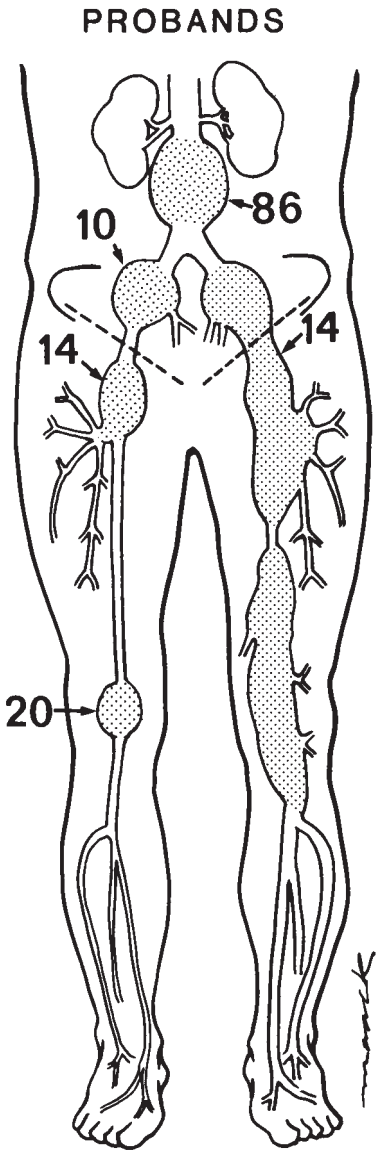

Fig 1. Distribution of aneurysms among the probands.

Table II. Distribution of aneurysms among probands

Type of aneurysm	*Total*	*Mean age (y)*	*No. of men*	*No. of women*	*M/F ratio*	*No. of patients with affected relatives*
Iliac	10	72	9	1	9	0 (0)
Femoral	14	68	14	0	∞	2 (14)
Popliteal	20	63	20	0	∞	2 (10)
Total peripheral	40*	67	43	1	43	4 (10)
Arteriomegaly	14	68	13	1	13	5 (36)
Abdominal aortic	86	70	73	13	5.6	19 (22)

Values in parentheses are percentages.
*Four patients had isolated aneurysms in two locations.

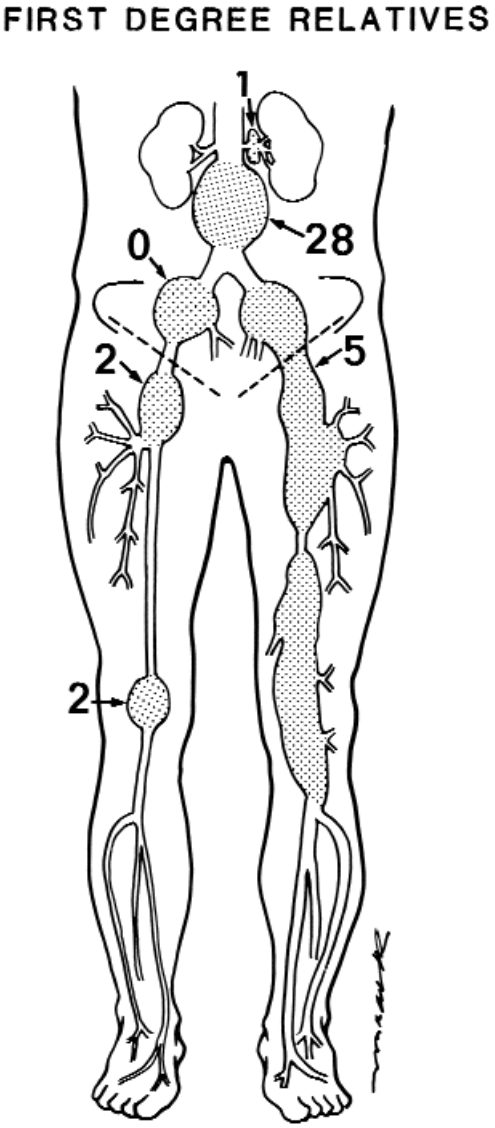

Fig 2. Distribution of aneurysms among primary relatives older than 50 years.

First-degree relatives. A total of 38 of the 703 primary relatives (5.4%) of patients with aneurysms also had an aneurysm (Fig 2); 28 (73%) of the aneurysms were aortic. As shown in Table IV, 36% of probands with arteriomegaly, 22% of probands with AAA, and 10% of patients with a peripheral aneurysm had a first-degree relative with an aneurysm. The risk that any individual family member had an aneurysm ranged from 7% for aortic aneurysm to 2% for peripheral aneurysm. There was no significant difference in risk factors, such as hypertension and diabetes, among first-degree relatives with aneurysms as compared with those without aneurysms.

It is of interest to note the location of aneurysms among the relatives (Table V). Irrespective of the site of aneurysms among the probands, aneurysms among relatives occurred predominantly in the aorta. The other common site of aneurysms among relatives was the femoral artery. Among 40 probands with peripheral aneurysms, 4 probands each had 1 relative with an aneurysm (2 aortic, 2 peripheral arterial aneurysm). Among 14 probands with arteriomegaly, 5 probands each had one relative with AAA; none had peripheral aneurysms. We were unable to determine how many relatives of arteriomegaly probands also had arteriomegaly, because this condition usually is diagnosed with angiography. For the 86 AAA probands, 28 relatives had AAA, 5 had arteriomegaly, and 4 had peripheral aneurysms.

Sex association. The prevalence of aneurysms was different for men and women among both the probands and first-degree relatives. For probands, 43 of 44 peripheral aneurysms occurred among men, 73 of 86 aortic aneurysms occurred among men, and 13 of 14 cases of arteriomegaly occurred among men. Because 44 of 140 of our probands were from the Veterans Affairs hospital, which predominantly cares for male patients, the high proportion of male probands may reflect the predominantly male veteran population. However, among first-degree relatives (Table VI), the proportion of men to women with aneurysms was similarly male dominated. The male-to-female ratios for first-degree relatives with an aneurysm ranged from 3:2 for arteriomegaly to 6:1 for AAA to infinity for peripheral arterial aneurysm. As seen in Table VI, the male-to-female ratio among first-degree relatives of AAA probands was 6. The individual risk for aneurysm among primary relatives was greater among men than among women.

Age association. Fig 3 shows the age at which aneurysms were found. Aneurysms among first-degree relatives were evaluated only for patients older than 50 years. Aneurysms occurred with increasing frequency from 56 to 75 years of age. After 75 years of age, there were fewer first-degree relatives alive, which may account for the decreasing absolute numbers.

DISCUSSION

Degenerative aneurysms of the peripheral arteries are believed to have a causation similar to that of aortic aneurysms.[13] However, several epidemiologic and clinical features of peripheral aneurysms suggest a different type of disease. Peripheral aneurysms occur almost exclusively among men, are frequently

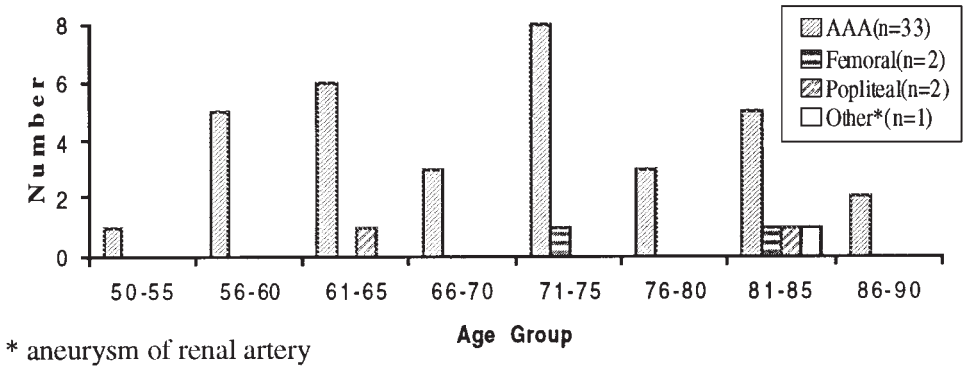

Fig 3. Age at which first-degree relatives manifested an aneurysm.

Table III. Risk factors among probands

Risk factor	*AAA (n = 86)*	*Peripheral (n = 40)*	*AAA with peripheral* (n = 12)*	*Arteriomegaly (n = 14)*	*P value*
Hypertension	43 (50)	24 (60)	10 (83.3)	9 (64)	NS
Smoking history	68 (79.1)	24 (60)	10 (83.3)	10 (71.4)	NS
Hypercholesterolemia	26 (30.2)	8 (20)	5 (41.7)	4 (28.5)	NS
COPD	16 (18.6)	7 (17.5)	2 (16.7)	0	NS
Inguinal hernia	34 (39.5)	5 (12.5)	5 (41.7)	6 (42.8)	< .01
Diabetes	7 (8.1)	11 (27.5)	1 (8.3)	0	< .01

Values in parentheses are percentages.
AAA, abdominal aortic aneurysm; *NS,* not significant; *COPD,* chronic obstructive pulmonary disease.
*Excluding patients with arteriomegaly.

bilateral, and thrombose or embolize rather than rupture.[14,15] Because of these differences, it is not clear that peripheral aneurysms have the same familial predilection demonstrated by several authors for aortic aneurysms.[16,17] Although several authors have attempted to demonstrate inheritance among some patients with aortic aneurysms,[18,19] candidate genes have not been confirmed by more than one institution. In addition, a disease that presents itself late in life, even when highly prevalent in one family, may have a multifactorial cause. The causes might be shared risk factors, such as hypertension, or social factors, such as smoking, rather than an inherited genetic defect that solely causes aneurysms.

Patients with a peripheral aneurysm have been demonstrated by several authors to have a synchronous peripheral aneurysm 20% to 50% of the time.[20,21] In our study, we only found a 10% prevalence of synchronous peripheral aneurysms, in spite of our policy of routine ultrasound surveillance or physical examination or both of both femoral and popliteal vessels for all patients with peripheral aneurysms. However, as did other authors, we did identify aortic aneurysms among 25% of patients with peripheral aneurysms, suggesting that aortic ultrasonography should be routine for these patients as well.

Table IV. Aneurysm risk among first-degree relatives

Proband	*Any first-degree relative**	*Risk per first-degree relative (%)*
Arteriomegaly	5/14 (36)	5.5
Abdominal aortic aneurysm	19/86 (22)	6.8
Peripheral aneurysm	4/40 (10)	2

Values in parentheses are percentages.
*Peripheral aneurysm versus abdominal aortic aneurysm $P = .16$; peripheral aneurysm versus arteriomegaly $P = .08$; arteriomegaly versus abdominal aortic aneurysm $P = .43$.

Our study raised several issues not previously reported. For example, 36% of patients with arteriomegaly had an affected first-degree relative. Thus arteriomegaly appears to be a strong predictor of familial aneurysms. AAA had a 22% incidence rate, and peripheral aneurysms had a 10% incidence rate. Because women comprise approximately one half of family members and peripheral aneurysms and arteriomegaly rarely occur among women, this makes

Table V. Distribution of aneurysms among first-degree relatives

		Location of aneurysms among first-degree relatives					
Proband aneurysm	*No. of relatives**	*Aortic*	*Iliac*	*Femoral*	*Popliteal*	*Other*	*Total*
Iliac (10)	56	0	0	0	0	0	0
Femoral (14)	58	1	0	2	0	0	3
Popliteal (20)	100	1	0	0	0	1†	2
Total peripheral (40‡)	202	2	0	2	0	1†	5
Arteriomegaly (14)	91	5	0	0	0	0	5
AAA (86)	410	24	0	3	1	0	28

Value in parentheses is number of patients.
*Relatives older than 50 years.
†Renal aneurysm.
‡Four patients had isolated aneurysms in two locations.

Table VI. Risk for aneurysm among first-degree relatives

		Relatives				
		Aneurysms		*Prevalence*		
Proband	*Total*	*Men*	*Women*	*Men*	*Women*	*M/F Ratio*
Iliac	56	0	0	0	0	0
Femoral	58	2	0	3.4	0	∞
Popliteal	100	2	0	2	0	∞
Total peripheral	204	4	0	2	0	∞
Arteriomegaly	91	3	2	3	2	1.5
Abdominal aortic	410	24	4	6	1	6

first-degree male relatives of patients with arteriomegaly particularly susceptible to this disease. A male relative of a patient with arteriomegaly had a 6.7% risk for a clinically significant aneurysm. Peripheral aneurysms, which frequently occur in other peripheral vessels in the same patient, occurred among 5% of first-degree male relatives and never among women. In spite of the seemingly high risk among immediate family members of patients with arteriomegaly and aortic aneurysms, it should be remembered that the risk is distributed over an average of 5 first-degree relatives, so the individual risk is much lower. Some families may have multiple individuals with an aneurysm. Four of 6 brothers of 1 proband in this study had symptomatic aneurysms at multiple sites, in spite of no known risk factors.

The likelihood that any first-degree relative of a proband would have a clinically significant aneurysm was 5.4%. This number is similar to the 5% prevalence of aneurysms among men older than 50 years in the European population, although many of the aneurysms in the general population would not be identified or treated because of their small size, whereas all our patients had an aneurysm large enough to necessitate repair. However, the 5.4% prevalence was higher than that reported by the Veterans Affairs Cooperative Trial. In addition, the 5.4% prevalence among first-degree relatives included both men, who have an higher prevalence of disease, and women, who have a very low prevalence of peripheral and aortic aneurysms.

One limitation of this study was that only patients with diagnosed or managed aneurysms were identified. To be certain that all aneurysms have been identified, a prohibitively expensive screening study of all patients and their relatives, as well as postmortem examinations of relatives, would be required. Such studies have been reported for probands and first-degree relatives of patients with aortic aneurysms, but not for families of patients with peripheral aneurysms.[22] These studies identified aneurysms among first-degree relatives, but most of these aneurysms were small and clinically insignificant at the time of identification, and some family members have been difficult to find and screen. If all first-degree relatives of patients with peripheral aneurysms (men and women older than 50 years) were screened for aneurysmal disease of the aortic and peripheral

vessels (aorta, iliac, femoral, popliteal), it would take 91 (arteriomegaly) to 500 (popliteal) normal ultrasound studies to diagnose a single aneurysm large enough to necessitate treatment.

These data led to the focus of this study: Should relatives of patients with peripheral aneurysms or arteriomegaly be screened for aneurysms? From our study it does not appear that risk factors can help identify relatives at high risk who should undergo screening. Ultrasound screening of all male and female first-degree relatives of patients with aneurysms is predicted to have a low yield and be quite expensive. However, selective ultrasonography should be useful. The aorta is the most important vessel to evaluate, because 70% of the aneurysms that were diagnosed in the relatives of probands with peripheral aneurysm were located in the abdominal aorta. This also holds true for patients with aortic aneurysms; 24 of 28 (85%) relatives with aneurysms had AAAs. A careful physical examination should help identify most peripheral aneurysms; therefore we emphasize physical examination as the most cost-effective method of identifying peripheral aneurysms and reserve ultrasound studies of peripheral vessels for obese patients and those with a questionable physical examination.

In our opinion, screening of the aorta by means of ultrasound examination should be performed for first-degree relatives of patients with aortic aneurysms and arteriomegaly but not peripheral aneurysms, because 6.8% of first-degree relatives of AAA probands were seen to have aneurysms, and 5.5% of first-degree relatives of arteriomegaly probands were seen to have aneurysms. Use of a selective screening strategy for relatives of patients with peripheral aneurysms and arteriomegaly may provide a more cost-effective method of ascertaining which family members are at higher risk for aneurysms than the general population. Limiting screening with physical examination and ultrasound scans to elderly, male first-degree relatives is more likely to be cost effective than any other approach.

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